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| 10/006,909 | 12/06/2001 | Jay Keasling | 2000-0007 | 1524 |

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REED & EBERLE LLP
800 MENLO AVENUE, SUITE 210
MENLO PARK, CA 94025

| EXAMINER | |
|---|---|
| FRONDA, CHRISTIAN L | |

| ART UNIT | PAPER NUMBER |
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| 1652 | |

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/006,909 | KEASLING ET AL. | |
| | Examiner | Art Unit | |
| | Christian L Fronda | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *24-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/02/02; 08/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restriction*

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-23, drawn to a method for synthesizing isopentenyl pyrophosphate in a host microorganism comprising introducing into the host microorganism a plurality of heterologous nucleic acid sequences encoding for a different enzyme in the mevalonate pathway, classified in class 435, subclass 132.

II. Claims 24-43, drawn to a method for synthesizing isopentenyl pyrophosphate in a host microorganism comprising introducing an intermediate in the mevalonate pathway and at least one heterologous nucleic acid sequence encoding for a different enzyme in the mevalonate pathway, classified in class 435, subclass 132.

III. Claims 44-60, drawn to an isolated DNA fragment, expression vector, and host cell, classified in class 435, subclass 252.3.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions III and I/II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product such as using the isolated DNA fragment, expression vector, and host cell in a process for recombinantly producing a polypeptide.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

3. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the

patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

4. During a telephone conversation with Shelley Eberle on April 27, 2004, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-23. Affirmation of this election must be made by applicant in replying to this Office action. Claims 24-60 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

6. Claims 1-23 are under consideration in this Office Action.

### *Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph*

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 13-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 13, the phrase "isopentenyl pyrophosphate is further modified to provide an isoprenoid" renders the claim vague and indefinite because it is no known or recited how the isopentenyl pyrophosphate is modified to provide an isoprenoid. Claims 14-21 which depend from claim 13 are also rejected because they do not correct the defect of claim 13.

Amending the claims to recite specific method steps leading to the production of the isoprenoid may overcome the rejection.

9. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: culturing the recited host microorganism in the presence of substrate under the appropriate conditions and time, and isolating the produced isopentenyl pyrophosphate.

### *Claim Rejections - 35 U.S.C. § 112, 1st Paragraph*

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-4, 6-8, 10, and 12-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

MPEP §2111 states that claims must be given their broadest reasonable interpretation consistent with the specification and that such interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. The claims of the instant invention must be read in light of the specification to thereby interpret limitations explicitly recited in the claims. Thus, limitations of the specification cannot be read into the claims to narrow the scope of the claims by implicitly adding disclosed limitations which are not recited in the claims.

According to the specification on page 7, lines 22-23, the mevalonate pathway is defined as a "pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate

In view of MPEP §2111 and page 7, lines 22-23 of the specification, claim 1 is deemed to be a genus claim which encompasses a genus of methods for preparing any isopentenyl pyrophosphate in any host microorganism, wherein any plurality of heterologous nucleic acids of any nucleotide sequence and structure encoding any enzyme of any amino acid sequence and structure encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate is introduced by any genetic method into the host microorganism. The recited plurality of heterologous nucleic acids is deemed contain at least two nucleic acids which encode enzymes encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate. Claim 13 is deemed to be a genus claim where the method of claim 1 is further modified where the isopentenyl pyrophosphate is father modified by an means to provide and isoprenoid.

The scope of claim 1 is highly variant and includes many heterologous nucleic acids with widely differing structural, chemical, biological, and physical characteristics which encode many heterologous enzymes that have widely differing structural, chemical, biological, and physical characteristics which are encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate.

The specification describes the production of the carotenoid lycopene using an E. coli strain transformed with the MEVT operon of SEQ ID NO: 8 and the MBI operon of SEQ ID NO: 12 and transformation of an E. coli strain MEVT operon of SEQ ID NO: 8 and MEVB operon of SEQ ID NO: 9, where the MEVT and MEVB operons contain a nucleic acid of SEQ ID NO:1 which encodes a acetoacetyl-coA thiolase, SEQ ID NO: 2 which encodes a HMG-CoA synthase, SEQ ID NO: 3 which encodes HMG-CoA reductase, SEQ ID NO: 4 which encodes mevalonate kinase, SEQ ID NO: 5 which encode phosphomevalonate kinase, and SEQ ID NO: 6 which encode mevalonate pyrophosphate decarboxylase

The specification does not provide a written description of any other members of the genus of heterologous nucleic acids with widely differing structural, chemical, biological, and physical characteristics which encode many heterologous enzymes that have widely differing structural, chemical, biological, and physical characteristics which are encompassed by any

pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate. The specification does not provide a written description of any of the enzymes recited in claims 10 and 14, other than SEQ ID NO: 1 which encodes an acetoacetyl-coA thiolase, SEQ ID NO: 2 which encodes a HMG-CoA synthase, SEQ ID NO: 3 which encodes HMG-CoA reductase, SEQ ID NO: 4 which encodes mevalonate kinase, SEQ ID NO: 5 which encodes a phosphomevalonate kinase, SEQ ID NO: 6 which encodes a mevalonate pyrophosphate decarboxylase, and SEQ ID NO: 10 which encodes isopentenyl pyrophosphate isomerase.

The method for making the carotenoid lycopene described in the specification, **is only representative** of a genus of methods for making isopentenyl pyrophosphate using the following transformed microorganisms: (1) a host microorganism transformed with the single operon of SEQ ID NO: 7; (2) a host microorganism transformed with both the MVET operon of SEQ ID NO: 8 and MEVB operon of SEQ ID NO: 9; (3) or a host microorganism transformed with the polynucleotides of SEQ ID NOS: 1-6, where SEQ ID NO: 1 encodes an acetoacetyl-coA thiolase, SEQ ID NO: 2 encodes a HMG-CoA synthase, SEQ ID NO: 3 encodes HMG-CoA reductase, SEQ ID NO: 4 encodes mevalonate kinase, SEQ ID NO: 5 encodes a phosphomevalonate kinase, SEQ ID NO: 6 encodes a mevalonate pyrophosphate decarboxylase, and SEQ ID NO: 10 which encodes an isopentenyl pyrophosphate isomerase.

The method for making the carotenoid lycopene described in the specification **is not representative** of the entire genus of claim 1 and claim 13, where claim 1 encompasses a genus of methods for preparing any isopentenyl pyrophosphate in any host microorganism, wherein any plurality of heterologous nucleic acids of any nucleotide sequence and structure encoding any enzyme of any amino acid sequence and structure encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate is introduced by any genetic method into the host microorganism, and claim 13 encompasses any method to make any isoprenoid from the produced isopentenyl pyrophosphate.

Thus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the genus of claim 1. Claims 2-4, 6-8, 10, and 12-23 which depend from claim 1 are also rejected because they do not correct the defect of claim 1.

Amending the claims to recite a method for making isopentenyl pyrophosphate using the following transformed microorganisms may overcome the rejection: (1) a host microorganism transformed with the single operon of SEQ ID NO: 7; (2) a host microorganism transformed with both the MVET operon of SEQ ID NO: 8 and MEVB operon of SEQ ID NO: 9; (3) or a host microorganism transformed with the polynucleotides of SEQ ID NOS: 1-6, where SEQ ID NO: 1 encodes an acetoacetyl-coA thiolase, SEQ ID NO: 2 encodes a HMG-COA synthase, SEQ ID NO: 3 encodes HMG-COA reductase, SEQ ID NO: 4 encodes mevalonate kinase, SEQ ID NO: 5 encodes a phosphomevalonate kinase, and SEQ ID NO: 6 encodes a mevalonate pyrophosphate

decarboxylase . Amending claim 13 to recite the proposed host microorganisms in addition to the specific method steps using specific enzymes to make the isoprenoid may overcome the rejection.

***Claim Rejections - 35 U.S.C. § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 12, 13, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoshino et al. [EP 0955363].

In view of MPEP §2111 and page 7, lines 22-23 of the specification, claim 1 is deemed to be a genus claim which encompasses a genus of methods for preparing any isopentenyl pyrophosphate in any host microorganism, wherein any plurality of heterologous nucleic acids of any nucleotide sequence and structure encoding any enzyme of any amino acid sequence and structure encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate is introduced by any genetic method into the host microorganism. The recited plurality of heterologous nucleic acids is deemed contain at least two nucleic acids which encode enzymes encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate.

Hoshino et al. [EP 0955363] teach a method for producing compounds involved in the mevalonate pathway including isopentenyl-pyrophosphate, isoprenoids, and carotenoids by using transformed host cells containing vectors or plasmids comprising genes encoding enzymes in the mevalonate pathway, where the enzymes encode by SEQ ID NOS: 1-5 are HMG-CoA synthase, HMG-CoA reductase, mevalonate kinase, mevalonate pyrophosphate decarboxylase, and farnesyl pyrophosphate synthase (see claims 1-10, abstract, entire publication, especially p. 2, paragraph [0003] to p. 4, paragraph [0016]). Hoshino et al. further teach that these genes may be transformed into a host such as E.coli and P. rhodozyma for the purposes of making the carotenoid astaxanthin (see p. 2, lines 48-55; and p. 4, lines 12-24).

Thus, the reference teachings anticipate the invention of claims 1, 12, 13, 22, and 23.

***Claim Rejections - 35 U.S.C. § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoshino et al. [EP 0955363] in view of Takagi et al. [Journal of Bacteriology, Aug 2000, p. 4153-4157]. The Takagi et al. reference is cited in the IDS dated April 02, 2002 as reference **BF**.

In view of MPEP §2111 and page 7, lines 22-23 of the specification, claim 1 is deemed to be a genus claim which encompasses a genus of methods for preparing any isopentenyl pyrophosphate in any host microorganism, wherein any plurality of heterologous nucleic acids of any nucleotide sequence and structure encoding any enzyme of any amino acid sequence and structure encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate is introduced by any genetic method into the host microorganism. The recited plurality of heterologous nucleic acids is deemed contain at least two nucleic acids which encode enzymes encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate.

The teachings of Hoshino et al. have been recited above. Hoshino et al. does not teach a method for preparing any isopentenyl pyrophosphate in any host microorganism, wherein any plurality of heterologous nucleic acids encoding any enzyme encompassed by any pathway that converts acetyl-CoA to isopentenyl pyrophosphate through a mevalonate intermediate is present in a single vector as recited in claims 3 and 4.

Takagi et al. teach an isolated DNA fragment containing a gene cluster for the mevalonate pathway from Streptomyces sp. Strain CL190 which is containing in a plasmid, and the plasmid is contained in a transformed E.coli host cell, wherein the gene cluster contains genes encoding HMG-CoA synthase, HMG-CoA reductase, mevalonate kinase, phosphomevalonate kinase, and mevalonate pyrophosphate decarboxylase (see entire publication).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Hoshino et al. by inserting the DNA fragment containing a gene cluster for the mevalonate pathway from Streptomyces sp. Strain CL190 taught by Takagi et al. into the plasmid contained in the transformed E.coli host cell for the purpose of making a transformed E.coli host cell to be used in the production of isopentenyl pyrophosphate. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because of the convenience of introducing a single fragment containing the entire gene cluster for the mevalonate pathway into a recombinant E.coli host cell. Thus, the invention of claims 3 and 4 was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly prima facie obvious.

***Conclusion***

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600